PATENT COOPERATION TREATY

From the:
INTER' 'TIONAL PRELIMINARY EXAMINING AUTHORITY

MONDAY 29 AUG 2005

To:

Davies Collison Cave
Level 15
1 Nicholson Street
MELBOURNE VIC 3000

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 26 AUG 2005
Applicant's or agent's file reference 12440340-EJH	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/AU2004/000524	23 April 2004	23 April 2003

Applicant

HEXIMA LTD et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide*.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	TERRY MOORE Telephone No. (02) 6283 2632

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12440340-E	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2004/000524	International filing date *(day/month/year)* 23 April 2004	Priority date *(day/month/year)* 23 April 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] C12N 9/76, 15/57, 15/12; A01H 5/00; A01N 63/00

Applicant

HEXIMA LTD et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
17 November 2004	23 August 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer TERRY MOORE Telephone No. (02) 6283 2632

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000524

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages 1-102 as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* 103-106 received by this Authority on 17 November 2004 with the letter of the same date
pages* received by this Authority on with the letter of

☒ the drawings:

pages 1/36-36/36 as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded"*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000524

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 15-26 (partially)

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. 15-26 (partially). See supplemental box.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14 (completely), 15-26 (partially)	YES
	Claims		NO
Inventive step (IS)	Claims	1-14 (completely), 15-26 (partially)	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The applicant's invention resides in the isolation of a chymotrypsin, HpCh5 (SEQ ID NO:2), from *Helicoverpa* spp. HpCh5 is characterised by its resistance to the proteinase inhibitors derived from *Nicotiana alata*.

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 Heath, R. L. et al., 1997, *Journal of Insect Physiology*, 43:833-842
D2 Bown, D. P. et al, 1997, *Insect Biochemistry and Molecular Biology*, 27:625-638.
D3 Gatehouse, L. N. et al., 1997, *Insect Biochemistry and Molecular Biology*, 27:929-944.
D4 Mazumdar-Leighton, S. & Broadway, R., 2001, *Insect Biochemistry and Molecular Biology*, 31:633-644.

Novelty (N) and Inventive Step (IS)

D1 describes production of proteinase inhibitors by *Nicotiana alata* and examines the insect's response when these inhibitors are incorporated into their diet. D2-D4 relate to the identification of inhibitor-insensitive protease genes from insect pests.

D1-D4 do not disclose the protein HpCh5. As such, the invention defined in claims 1-45, 47, 48 meets the requirements of Article 33(2) PCT with regard to novelty. Furthermore, the present claims meet the criteria set out in PCT Article 33(3) with regard to the requirement of Inventive Step because the prior art does not obviously suggest to a person skilled in the art the presence of HpCh5 (SEQ ID NO: 2), a chymotrypsin that exhibits resistance to the proteinase inhibitors derived from *Nicotiana alata*.

Industrial Applicability (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1) Claims 1, 3, 5-9, and 13-15 are not fully supported by the description.

The applicant's invention resides in the isolation of a chymotrypsin (HpCh5; SEQ ID NO: 2) from *Helicoverpa* spp that exhibits resistance to the serine proteinase inhibitors of *Nicotiana alata*. With respect to derivatives or variants of said protein, it is considered that the applicant's invention is limited to those proteins that display the same function as HpCh5, namely chymotrypsin activity and resistance to the serine proteinase inhibitors of *Nicotiana alata*, and the encoding nucleic acid molecules. Claims 1, 3, 5-9, and 13-15 are not limited to protein variants that display chymotrypsin activity and resistance to the serine proteinase inhibitors of *Nicotiana alata*, hence the claims are not fully supported by the description.

2) Claims 15-26 are not fully supported by the description because the claims are not limited to antagonists, agents or inhibitors that are produced using the applicant's invention.

The applicant's invention resides in the isolation of a chymotrypsin (HpCh5; SEQ ID NO: 2) from *Helicoverpa* spp that exhibits resistance to the serine proteinase inhibitors of *Nicotiana alata*. As such the applicant is entitled to claim HpCh5 and derivatives thereof for example antibodies, antisense, ribozymes, methods of using said derivatives, and compounds produced by the use of HpCh5.

Claims 15-26 relate to an inhibitor of HpCh5 identified using an active chymotrypsin wherein said chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence having at least about 75% similarity to SEQ ID NO: 2. As discussed previously, this is not a claim to a derivative of HpCh5 or a compound produced by the use of HpCh5. Rather the claims encompass any independent compound that inherently antagonises HpCh5 and whose engineering or isolation owes nothing to the teachings of the patent application. A method of identification does not produce a product, it merely provides new information about a pre-existing compound, thus the claim defines a compound *per se*, not a product of the applicant's invention. As such, the claims are not fully supported by the description.

It is noted that inhibitors of the activity of the proteins of the invention would be acceptable if they were limited to inhibitors isolated using the polynucleotides or proteins of the invention, or inhibitors derived from HpCh5 for example antibodies, antisense and ribozymes.

3) Claims 19-26 are not fully supported by the description.

The claims define a genetically modified plant comprising cells capable of producing an inhibitor of a chymotrypsin as defined in any one of claims 15-17. With respect to cells that are capable of producing an inhibitor of a chymotrypsin, the present specification only provides support for a transgenic plant comprising a transgene that expresses the inhibitor. Therefore, in the absence of limitation of the claims such that they are restricted to transgenic plants comprising a transgene that expresses the inhibitor of chymotrypsin as defined in any one of claims 15-17, the claims lack full support.

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   - [X] a sequence listing
   - [ ] table(s) related to the sequence listing

   b. format of material

   - [ ] in written format
   - [X] in computer readable form

   c. time of filing/furnishing

   - [X] contained in the international application as filed
   - [ ] filed together with the international application in computer readable form
   - [ ] furnished subsequently to this Authority for the purposes of search and/or examination
   - [ ] received by this Authority as an amendment* on

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III (Non-establishment of opinion with regard to novelty, inventive step and industrial applicability)

The claims equivalent to claims 15-26 were only partially searched in the ISR because the scope of the claims is so inadequately supported by the specification that a meaningful search covering the full scope of the claims could not be carried out.

Claim 15 is directed to an inhibitor of a chymotrypsin identified using an active chymotrypsin from *Helicoverpa* spp. wherein said chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence having at least about 75% similarity to SEQ ID NO: 2.. This is not a claim to a derivative of HpCh5 (SEQ ID NO: 2) or a compound produced using HpCh5, it is a claim that encompasses an independent compound that inherently inhibits HpCHh5 and whose engineering or isolation owes nothing to the teachings of the patent application. Thus the claim may encompass known substances inherently possessing the stated properties. No meaningful search could be performed on the full scope of the claim 15, or appended claims 16-26, hence the present opinion relates to claims 15-26 to the extent that the claims have been searched. Thus with respect to claims 15-26 the present opinion covers the claims in so far as they relate to derivatives of HpCh5 (eg antisense, antibodies) that antagonise its activity or expression (claims 15-18), and transgenic plants comprising cells capable of producing these inhibitors (claims 19-26).

1. Use of an active or activatable chymotrypsin from *Helicoverpa* spp., or an active or activatable variant or homolog of said chymotrypsin wherein said chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO:2 or an amino acid sequence having at least about 75% similarity to SEQ ID NO:2 after optimal alignment in the manufacture of an inhibitor of said chymotrypsin.

2. Use of Claim 1 wherein the chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO:2.

3. Use of Claim 1 wherein the chymotrypsin is encoded by a nucleotide sequence as set forth in SEQ ID NO:4 or SEQ ID NO:6 or a nucleotide sequence having at least about 75% identity to SEQ ID NO:4 or SEQ ID NO:6 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:4 or SEQ ID NO:6 or its complementary form under low stringency conditions.

4. Use of Claim 3 wherein the nucleotide sequence is as set forth in SEQ ID NO:4.

5. Use Claim 1 wherein the variant of the chymotrypsin comprises an N-terminal signal sequence which comprises an amino acid sequence set forth in SEQ ID NO:3 or an amino acid sequence having at least about 75% similarity to SEQ ID NO:3 after optimal alignment.

6. Use of Claim 5 wherein the variant chymotrypsin is encoded by a nucleotide sequence as set forth in SEQ ID NO:5 or a nucleotide sequence having at least 75% identity to SEQ ID NO:5 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:5 or its complementary form under low stringency conditions.

7. Use of Claim 1 wherein the variant of the chymotrypsin comprises an amino acid other than arginine at position 192.

8. Use Claim 7 wherein the variant of the chymotrypsin comprises a glutamine at position 192.

9. Use of an expression system encoding an active or activatable chymotrypsin from *Helicoverpa* spp., or an active or activatable variant or homolog of said chymotrypsin wherein the chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO:2 or an amino acid sequence having at least about 75% similarity to SEQ ID NO:2 after optimal alignment in the manufacture of an active chymotrypsin.

10. Use of Claim 9 wherein the expression system comprises a nucleotide sequence which encodes an amino acid sequence set forth in SEQ ID NO:2.

11. Use of Claim 9 wherein the expression system comprises a nucleotide sequence as set forth in SEQ ID NO:4 or SEQ ID NO:6 or a nucleotide sequence having at least about 75% identity to SEQ ID NO:4 or SEQ ID NO:6 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:4 or SEQ ID NO:6 or its complementary form under low stringency conditions.

12. Use of Claim 11 wherein the nucleotide sequence is as set forth in SEQ ID NO:4.

13. Use Claim 9 wherein the variant of the chymotrypsin comprises a variant is the N-terminal signal sequence which comprises an amino acid sequence set forth in SEQ ID NO:3 or an amino acid sequence having at least about 75% similarity to SEQ ID NO:3 after optimal alignment.

14. Use of Claim 13 wherein the variant chymotrypsin is encoded by a nucleotide sequence as set forth in SEQ ID NO:5 or a nucleotide sequence having at least 75% identity to SEQ ID NO:5 after optimal alignment or a nucleotide sequence capable of hybridizing to SEQ ID NO:5 or its complementary form under low stringency conditions.

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15. An isolated inhibitor of a chymotrypsin said inhibitor identified using an active or activatable chymotrypsin from *Helicoverpa* spp., or an active or activatable variant or homolog of said chymotrypsin wherein said chymotrypsin comprises an amino acid sequence set forth in SEQ ID NO:2 or an amino acid sequence having at least about 75% similarity to SEQ ID NO:2 after optimal alignment.

16. The inhibitor of Claim 15 wherein the inhibitor binds or interacts with the chymotrypsin at or near amino acid residue position 192.

17. The inhibitor of Claim 15 or 16 wherein said inhibitor is PotI.

18. A genetically modified plant comprising cells capable of producing an inhibitor of a chymotrypsin as defined in any one of Claims 15 to 17.

19. The genetically modified plant of Claim 18 wherein the plant is a monocotyledonous plant.

20. The genetically modified plant of Claim 18 wherein the plant is a dicotyledonous plant.

21. The genetically modified plant of Claim 18 wherein the plant is a crop plant, vegetable plant or ornamental plant or tree.

22. The genetically modified plant of Claim 18 wherein the plant produces PotI.

23. The genetically modified plant of Claim 18 wherein the plant is cotton, sweet corn, tomato, tobacco, piniento, potato, sunflower, citrus, plums, sorghum, leeks, soybean, alfalfa, beans, pidgeon peas, chick peas, artichokes, curcurbits, lettuce, *Dianthus* (an ornamental plant), geraniums, cape gooseberry, maize, flax and linseed, alfalfa, lupins,

broad beans, garden peas, peanuts, canola, snapdragons, cherry, sunflower, pot marigolds, *Helichrysum* (an ornamental plant), wheat, barley, oats, triticale, carrots, onions, orchids, roses and petunias.

24. The genetically modified plant of Claim 23 wherein the plant is a cotton plant.

25. The genetically modified plant of any one of Claims 18 to 24 comprising a nucleic acid molecule encoding Pot1A and/or Pot1B.

26. Seeds or other reproduction material from the plant of any one of Claims 18 to 25.